extrapyramidal syndromes than those treated with low-potency agents such as thioridazine. Low doses of neuroleptic agents generally lower the incidence and severity of the disorders. Dystonia, unfortunately, can appear at low antipsychotic doses and may be recurrent so that, even at low antipsychotic doses, prophylaxis may be needed.

Several circumstances may make the development of extrapyramidal syndromes especially undesirable. Paranoid patients for whom the therapeutic relationship is tenuous are one example. The development of these syndromes would be particularly harmful in patients requiring orthopedic devices such as neck braces or casts. These considerations should enhance the prescribing of prophylaxis. On the other hand, this prophylaxis is relatively contraindicated in patients who may be harmed by anticholinergic side effects such as impaired recent memory. Older patients receiving low-potency antipsychotic agents are unlikely to benefit from prophylaxis. Patients with deficits in short-term memory from head trauma, dementias, and other causes are not good candidates for prophylaxis as they are more likely to suffer further memory impairment and may become delirious.

The withdrawal of prophylactic medication should be attempted after the initial treatment has been completed if the patient is free of symptoms and the antipsychotic regimen has been stabilized. Studies have shown that some patients will have recurrent episodes and deterioration of mental status when anticholinergic therapy is withdrawn. For this reason, the withdrawal of prophylactic agents should be gradual and carefully monitored.

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REFERENCES

Arana GW, Goff DC, Baldessarini RJ, Keepers GA: Efficacy of anticholinergic prophylaxis for neuroleptic-induced acute dystonia. Am J Psychiatry 1988; 145:993-996

Casey DE, Keepers GA: Neuroleptic side effects: Acute extrapyramidal syndromes and tardive dyskinesia, *In* Christensen AV, Casey DE (Eds): Current Trends in Psychopharmacology. New York, NY, Springer-Verlag, 1988, pp74-93

Keepers GA, Casey DE: Use of neuroleptic-induced extrapyramidal symptoms to predict future vulnerability to side effects. Am J Psychiatry 1991; 148:85-89

Panic Disorder

THOUGH PANIC DISORDER and panic disorder with agoraphobia or phobic avoidance (PDA) are common (the mean lifetime prevalence of panic disorder is 1.5%), the diagnosis is frequently missed: 70% of patients with PDA in one large study had more than ten medical consultations before receiving the correct diagnosis and treatment.

The "classic" presentation of panic disorder consists of sudden, unexpected, discrete attacks of intense fear or discomfort without a recognizable precipitant, accompanied by at least four of the following symptoms during at least one of the attacks: dyspnea or smothering sensations; dizziness, unsteadiness, or faintness; palpitations or tachycardia; trembling or shaking; sweating; choking; nausea or abdominal distress; depersonalization or derealization; numbness or paresthesias; flushes or chills; chest pain or discomfort; fear of dying; and fear of going crazy or doing something uncontrolled. Panic disorder, however, frequently occurs with symptoms referable to only a single organ system. Such single system presentations include chest pain and dyspnea (33% to 59% of patients seen because of chest pain but with no abnormalities found on coronary angiography were found in three different studies to have PDA); balance disorder ("dizziness") without true vertigo (25% to 50% of patients seen because of vestibular disorder symptoms have a subtype of panic disorder); abdominal discomfort, pain, and diarrhea (about 33% of patients seen by gastroenterologists were found to have PDA).

Large-scale clinical studies have shown that for most patients, PDA is a chronic relapsing disorder. Multiple family and twin studies show that panic disorder has a highly familial transmission with a strong genetic component (31% monozygotic concordance, 0% dizygotic concordance).

Panic disorder with agoraphobia has a startlingly high comorbidity and mortality. Patients with untreated PDA attempt suicide at a rate equivalent to that of patients with major depression (15% to 20% of patients). This disorder has a dramatically high incidence of comorbid major depression, alcohol abuse, substance abuse, other anxiety disorders, multiple phobias or agoraphobia, cardiovascular disease, and personality disorders. Patients with PDA experience substantially more impairment in social, family, and occupational functioning than the general population.

The proven standard of effective treatment for PDA continues to be pharmacotherapy to stop and prevent recurrent panic attacks, plus behavior therapy (exposure in vivo) for any phobic avoidance that may remain once the panic attacks have been stopped. Most clinical studies have found the first-generation tricyclic antidepressants, the monoamine oxidase inhibitors, and two of the benzodiazepines (alprazolam [Xanax] and clonazepam [Klonopin]) highly effective in stopping and preventing recurrent panic attacks when maintained at therapeutic blood concentrations. Of the newer antidepressant medications, fluoxetine (Prozac) and clomipramine hydrochloride (Anafranil) have demonstrated efficacy in PDA, whereas buproprion hydrochloride (Wellbutrin) and the nonbenzodiazepine anxiolytic buspirone hydrochloride (BuSpar) have not.

The goal of appropriate pharmacologic management is the complete absence of all panic and subpanic attacks. This can be achieved with a single medication in more than 85% of patients, though it may take several treatment trials to find the best medication. Refractory cases may require more complicated protocols.

Recent reports of two nonpharmacologic treatments, cognitive therapy and cognitive-behavioral therapy, show promise for some patients with PDA.

The core of cognitive-behavioral treatment is systematic structured exposure to the feared internal sensations, coupled with cognitive procedures to restructure anxiety-provoking thoughts, catastrophic misinterpretations, and faulty core beliefs. The therapist directs the patient to induce the somatic sensations typical of a panic attack (dizziness, tachycardia, dyspnea, chest tension) in the office (by having the patient spin around, run in place, hyperventilate, or contract chest muscles tightly), while together therapist and patient critically examine the symptom experience, correct the patient's frightening and catastrophic cognitive misinterpretations of the sensations, and control the symptoms with a variety of relaxation techniques. The patient practices at home what is learned in the office and keeps a daily diary of symptoms, reflex cognitive distortions, and corrective thinking and behavior.

Reports of the nonpharmacologic treatment of PDA to date review small treatment populations and short follow-up

periods. The few studies comparing the efficacy (short- and long-term) of pharmacologic and nonpharmacologic treatments suffer from a variety of conceptual and methodologic difficulties. These include a failure to differentiate patients with panic disorder from those with panic disorder and agoraphobia or those with subtypes of panic disorder, and the heterogeneity of diagnostic criteria, treatment procedures, and measures of clinical success. Thus, our present state of knowledge does not enable us to predict accurately which patients will do best with which treatment(s) or how different treatments might best be integrated.

Patients with PDA should be educated regarding the various treatment options available. The choice of treatment will depend on the training and expertise of the clinician, the availability of specialists, a patient's sense of urgency, available resources, and the preferred type of treatment. If nonpharmacologic treatment is elected, those patients who are not completely relieved of panic attacks after an adequate treatment trial (three months), or who relapse after treatment, should receive appropriate pharmacologic therapy for panic, combined with exposure treatment of phobic avoidance.

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REFERENCES

Barlow DH: Long-term outcome for patients with panic disorder treated with cognitive-behavioral therapy. J Clin Psychiatry 1990; 51(SupplA):17-23

Kahn DG: Current trends in short-term therapeutic approaches to panic disorder. Int J Short-Term Psychother 1990; 5:211-245

Klosko JS, Barlow DH, Tassinari R: A comparison of alprazolam and behavior therapy in treatment of panic disorder. J Consult Clin Psychol 1990; 58:77-84

Michelson L, Marchione K, Greenwald M, Glanz L, Testa S, Marchione N: Panic disorder: Cognitive-behavioral treatment. Behav Res Ther 1990; 28:141-151

Pollack MH, Otto MW, Rosenbaum JF, et al: Longitudinal course of panic disorder: Findings from the Massachusetts General Hospital Naturalistic Study. J Clin Psychiatry 1990; 51(SupplA):12-16

Rational Polydrug Use in Psychiatry

SINGLE-DRUG THERAPY has been the standard for psychopharmacology for the past two decades. This approach is based on clinical studies that excluded multiple drug therapies to decrease variance in the results. There is consensus, however, that 20% to 40% of patients with depression, manic-depressive illness, anxiety disorders (panic disorder and obsessive-compulsive disorder), and schizophrenia either do not respond initially or do not maintain a response to standard single-drug regimens.

Few double-blind placebo-controlled studies have tested polydrug regimens because a large number of patients would be required to achieve statistical significance. We have to rely mainly on case series and reports based on pharmacologic theory or empiric findings. The reasons to use several drugs include a nonresponse to monodrug therapy; the need for imminent clinical remission (from either patient suffering or the financial limitations of waiting for serial therapies to work); the different therapeutic sites of action of multiple agents; additive or multiplicative effects; and the avoidance of side effects. For example, acute mania appears to respond faster, with better patient compliance, and with fewer side effects when a potent benzodiazepine (usually lorazepam or clonazepam) is temporarily added to a regimen of neuroleptic and antimanic agents. In labile manic-depressive illness, prophylaxis with an anticonvulsant (valproate or carbamazepine) or verapamil enhances stability.

Patients with depression that does not abate in three to four weeks with standard antidepressant therapy commonly will have lithium, thyroid, or stimulants added to the regimen. These agents work independently, and several may be used for refractory cases. Some antidepressants produce side effects that can be countered by others. Because the therapeutic effect is additive, two antidepressant heterocyclic reuptake inhibitors can be administered concurrently. This is commonly done when agitation or insomnia occurs with the use of fluoxetine or desipramine by adding trazodone or another sedating agent, such as doxepin or amitriptyline, at night. Although panic disorder often responds to the use of a single agent (such as alprazolam, phenelzine sulfate, or imipramine hydrochloride), subtle fluctuations in anxiety may continue and increase anticipatory anxiety to a disabling degree. Hence, adding the other agent(s), which act through separate mechanisms, is frequently required. A pharmacologic plateau of obsessive-compulsive disorder to the use of clomipramine or fluoxetine may take 12 weeks to occur, with a third of patients not responding. Serotoninergic activity is augmented by adding the other primary drug or buspirone hydrochloride (as much as 100 mg per day), lithium, or fenfluramine hydrochloride.

Schizophrenia is not a unitary disease, but neuroleptics all appear to have equivalent efficacy. Polydrug therapy with older neuroleptics plus clozapine has increasing appeal but few data to support its use. Neuroleptic side effects contribute importantly to noncompliance and morbidity, however. In addition to the well-appreciated use of anticholinergics, the recent understanding of akathisia has led to a low threshold for the use of propranolol hydrochloride (20 to 80 mg per day in divided doses) for this extrapyramidal syndrome of anxiety and motor restlessness. The augmentation of neuroleptic therapy has proved beneficial with the use of carbamazepine, lithium, or benzodiazepines in some schizophrenic patients. Although no specific subgroup is predictably responsive, it is commonly thought that these drugs are relatively more effective in patients with active psychotic symptoms, aggression, or schizoaffective schizophrenia.

The use of several hypnotic agents in a single patient is usually based on their half-life. In selected patients with pronounced difficulty falling and staying asleep, an ultrashort-acting hypnotic (triazolam, for instance) may be beneficial when combined with a longer-acting agent, and the combination has reduced morning sedative side effects.

In these uses of polydrug therapy, each agent is prescribed systematically and for a specific target behavior that can be evaluated for response. This rational use of multiple drugs is therefore valid. It is distinct from older, fixed-dose combination drugs or simplistically adding virtually identical agents without careful reasoning. The search for therapeutic benefit must be tempered by caution about additive side effects such as anticholinergic or hypotensive effects.

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REFERENCES

Gerner RH, Rosenlicht N: Systematic approaches to treatment resistant depression, *In* Amsterdam JD (Ed): Pharmacotherapy of Depression. New York, NY, Marcel Dekker, 1990, pp 381-400

Goodman WG, McDougle CJ: Serotonin reuptake inhibitors in the treatment of obsessive compulsive disorder. Ann Clin Psychiatry 1990; 2:173-181

Post RM: Anticonvulsants for the lithium-resistant bipolar patient, *In* Amsterdam JD (Ed): Pharmacotherapy of Depression. New York, NY, Marcel Dekker, 1990, pp129-158